effect (3.2, 2.5-4.2) respectively. The SI score for interaction was 3.6 (95% CI: 3.1-4.2).
Conclusions: Our study demonstrates that a familial propensity to SCA interacts with presence of increasing metabolic RF, magnifying the risks for those exposed to both.

1028-168 Is Asymmetric Dimethylarginine a Marker for Diabetes, Coronary Artery Disease, and Death/Myocardial Infarction? Results of the Intermountain Heart Collaborative Angiographic Registry Study

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Background: Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of nitric oxide synthase that has generated interest as a potential cause or marker of endothelial dysfunction and its clinical consequences, including diabetes, coronary artery disease (CAD), and renal failure.
Methods: We tested whether ADMA distinguishes patients (pt) with normal (NFG; <110 mg/dL), or impaired fasting glucose (IFG; 110-125), and diabetes (DM; ≥126 mg/dL); angiographic CAD; and death (D) or nonfatal myocardial infarction (MI) in a case-control cohort of 442 pt selected from the 3 glycemic categories from among 3000 pt entered in the Intermountain Heart Collaborative Registry. Consenting pt had fasting blood drawn for FG and ADMA during angiographic assessment and were followed for 2.6 ± 1.4 y. ADMA was assayed from cryogenically stored samples by high-pressure liquid chromatography with pre-column derivitzation and fluorescence detection. Non-parametric (KW) testing compared ADMA among groups. Logistic regression was used for predictive modeling.
Results: The study cohort consisted of equal numbers with NFG (146), IFG (148), and DM (148), matched for age (±5 y) and gender. Overall, age averaged 61 years; 72% were male; 24%, smokers; 68% had angiographic CAD; 61%, hypertension; 58%, hyperlipidemia; 24%, prior MI. During follow-up, 137 events occurred. Distribution of ADMA was broad and rightward skewed, with median 0.85 μM (range, 0-30). Mean (median) ADMA levels increased progressively by glycemic category (p<0.001): NFG=2.3 (0.74), IFG=3.0 (0.77), DM= 3.4 (1.27). When adjusted for standard risk factors, CAD severity, and presenting diagnosis, ln ADMA independently predicted DM (odds ratio [OR] 1.29 /ln unit, CI 1.07-1.54, p=0.006) and, less strongly, CAD (OR 1.21, CI 1.0-1.5, p=0.06). Ln ADMA trended higher in those with D/MI (adjusted OR 1.17, CI 0.98-1.39, p=0.08).
Discussion: Among a high coronary risk case-control cohort, ↑ADMA predicted ↑risk of IFG, DM, and CAD. Thus, ADMA might contribute to endothelial dysfunction associated with these conditions. Further research should determine whether ADMA is a causal factor or passive marker and determine causes of interpatient variability.

1028-169 The Predictive Value of Parental History of Coronary Disease

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Background: Parental history of coronary disease (CHD) is a well-known risk factor for CHD. However the risk conferred by the gender of an affected parent is controversial and data are sparse. This prospective study in high risk families was designed to determine the extent to which a maternal or paternal history of CHD contributed independently to the risk of incident CHD after adjusting for known risk factors.
Methods: Unaffected siblings (SIBS) of probands were identified from hospitalized index cases with a documented CHD event < 60 years of age. This prospective analysis includes 345 women and 339 men with either maternal, paternal or no parent with history of CHD. Parental family history was elicited by self-report and confirmed by another family member. SIBS were followed for incident CHD events. SIB events were documented by medical records and adjudicated by an external endpoints committee.
Results: The 684 SIBS were 46±7 yrs old at baseline, 50% female, 21% African American, 32% smokers, 7% diabetics, 43% hypertensives, and 67% hypercholesterolemic. Incident CHD occurred in 84/684 (12.3%) of all SIBS over 8.7±3.2 yrs follow-up. Incident events occurred in 12.9% of SIBS with no parental history, 10.5%; of sibs with a paternal history only, and 14.8% of SIBS with a maternal CHD history only. In a Cox proportional hazard analysis predicting incident CHD in SIBS, the multivariate adjusted relative risk for maternal CHD was 2.05 (95% CI=1.15-3.65) and for paternal history was 1.0 (95% CI=0.6-1.66), controlling for age, SIB sex, race, hypertension, current smoking, LDL cholesterol, diabetes, obesity and education.
Conclusion: Among individuals with a documented family history of premature CHD, having a maternal history of CHD was most strongly associated with the highest risk of a CHD event. Controlling for known risk factors, maternal history alone conferred a significant and independent excess risk of incident CHD whereas paternal alone history was not significant.

1028-170 Higher Levels of Lipoprotein-Associated Phospholipase A2 Are Associated With Higher Incidence of Cardiovascular Events at Follow-Up Independent of C-Reactive Protein

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Background: Limited data exist on the association between lipoprotein-associated phospholipase A2 (Lp-PLA2) with cardiovascular risk.
Methods and Results: We measured Lp-PLA2 levels in 504 consecutive patients undergoing clinically indicated coronary angiography. Mean age was 60±11 years and 38% were women. The mean (± SD) Lp-PLA2 level (ng/mL) was 245 ± 91. Median C-reactive protein (CRP, mg/L) was 0.29 (interquartile range: 0.12, 0.67). During a median follow-up of 4.0 years, 58 cardiovascular events occurred in 49 of 466 contacted patients (11%): cardiac death in 6, acute myocardial infarction (AMI) in 14, coronary revascularization in 28, and stroke in 10. Higher Lp-PLA2 levels were associated with a greater risk of cardiovascular events: the hazard ratio (HR) per standard deviation was 1.31 (p=0.010), and remained significant after adjusting for clinical (age, gender, smoking, hypertension) and lipid (total and HDL cholesterol, Lp(a), and triglycerides) variables and CRP (Table).
Conclusion: Higher Lp-PLA2 levels were associated with a higher incidence of cardiovascular events at follow-up, independently of traditional coronary artery disease risk factors and CRP.

Multivariate association between Lp-PLA2 and CRP with cardiovascular events at follow-up.

Endpoint	Lp-PLA2 HR (95% confidence intervals)	logCRP HR(95% confidence intervals)
Cardiac Death + AMI	1.31 (0.94, 1.81)	1.14 (0.73, 1.79)
Cardiac Death + AMI + Stroke	1.33 (1.02, 1.74)	1.26 (0.86,1.84)
Cardiac Death + AMI + Revascularization	1.25 (0.96, 1.64)	1.20 (0.88, 1.64)
Cardiac Death + AMI + Revascularization + Stroke	1.29 (1.02, 1.63)	1.26 (0.95, 1.67)
All-Cause Death + AMI	1.30 (1.01, 1.67)	1.35 (0.96, 1.89)
All-Cause Death + AMI + Stroke	1.32 (1.06, 1.65)	1.39 (1.03, 1.89)
All-Cause Death + AMI + Revascularization	1.28 (1.02, 1.61)	1.30 (0.99, 1.70)
All-Cause Death + AMI + Revascularization + Stroke	1.31 (1.06, 1.60)	1.34 (1.04, 1.72)

1028-171 Fasting Blood Glucose: An Underestimated Risk Factor for Subclinical Coronary Atherosclerosis

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Background: Non-diabetic individuals with high fasting blood glucose (FBG) are at high risk for experiencing the metabolic syndrome, which includes insulin resistance, hypertension, dyslipidemia, and a procoagulant state. While emerging evidence suggests that impaired FBG (FBG_110 mg/dl) may accelerate atherosclerosis, we sought to evaluate the independent impact of FBG in the upper normal range (<110 mg/dl) as a risk factor for subclinical coronary atherosclerosis assessed by coronary artery calcification (CAC) in an asymptomatic non-diabetic population.
Methods : We studied 531 consecutive asymptomatic, non-diabetic males (46±7 yrs; range 29-65 yrs) with FBG<110 mg/dl in the study who presented for electron-beam computed tomography (EBCT) between 1999 and 2002 in Sao Paulo, Brazil. The population was divided into 2 categories; highest quartile of FBG (>85 mg/dl, n=119) and the lowest three quartiles (n=412).
Results:Individuals in the highest quartile of FBG were more likely to have higher body mass index (28±4 vs. 26±3, p<0.0001), waist to hip ratio (0.99±0.06 vs. 0.93±0.06, p=0.01), triglycerides (410±116 vs. 180±92, p=0.05) and systolic blood pressure (131±14 vs.121±13, p<0.0001), where as no significant difference was observed in high density lipoprotein, low density lipoprotein and total cholesterol levels respectively. Overall median, 75th percentile and 90th percentile CAC scores were: 3, 24 and 156 among individuals with highest FBG quartile compared to 0, 6 and 56 among patients with lowest three quartiles (p<0.05). After adjusting for potential cofounders, the odds ratio for any calcification (CAC>0) with FBG>85 mg/dl was 2.5 (95% CI=1.1-5.4, p=0.02) and 1.8 (1.1-3.2, p=0.01) for ≥75th percentile CAC, respectively
Conclusions: FBG in the upper normal range (>85 mg/dl) appears to be an important independent predictor of presence and severity of CAC in non-diabetic apparently healthy young/middle aged men.

1028-172 Increased Urinary 8-Iso-Prostaglandin F2alpha Excretion Predict Cardiac Events in Patients With Type 2 Diabetes

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Background: Increased oxidant stress may play a key role in the etiology of diabetic cardiovascular complications. We hypothesized that increased production of 8-iso-prostaglandin F2alpha (8-iso-PGF2alpha), a marker for in vivo oxidant stress, predicts future cardiac events in type 2 diabetic patients.
Methods: We studied 148 patients aged 30-85 (62±10) with type 2 diabetes. Baseline level of urinary 8-iso-PGF2alpha excretions were measured and the patients were followed up for a mean period of 1380 days. Cardiac events were defined as hospitalization for acute myocardial infarction, unstable angina, revascularization, and worsening heart failure.
Results: One hundred thirty-nine patients completed the follow-up, while 2 died of noncardiac causes. Of the remaining 137 patients, cardiac events were occurred in 16. Urinary 8-iso-PGF2alpha excretion above the median value of 287.5 pg/mg creatinine was

associated with higher incidence of cardiovascular events (20% vs. 4%, p=0.004). Previous cardiovascular disease, defined as history of ischemic heart disease and/or peripheral vascular disease, was also associated with higher incidence of cardiovascular events (25% vs. 6%, p=0.003). Urinary 8-iso-PGF2alpha excretion above the median value was associated with cardiovascular events in this high-risk group (43% vs. 5%, p=0.007), but was not in the remaining "low-risk" diabetic patients (9% vs. 4%). In Cox regression analysis adjusting for age, gender, body mass index, glycemic control, and traditional risk factors, urinary 8-iso-PGF2alpha excretion (p=0.01) and previous cardiovascular disease (p=0.04) were independent predictors of cardiac events.
Conclusion: Increased urinary 8-iso-PGF2alpha excretion predicts cardiac events in patients with diabetes, especially in the group with overt cardiovascular disease. These results suggest that the assessment of urinary 8-iso-PGF2alpha excretion has clinical implications as a tool for risk stratification in patients with type 2 diabetes.

1028-173 Association Between Cardiorespiratory Fitness and C-Reactive Protein in Young Adults

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Background: Physical activity is associated with a lower risk of cardiovascular disease but the mechanisms remain uncertain. Inflammatory markers are predictive of cardiovascular risk. We therefore examined the association between cardiorespiratory fitness and C-reactive protein (CRP) in a group of young adults.
Methods: Cardiorespiratory fitness using a bicycle ergometer, blood pressure, smoking history, and anthropometric measurements were determined in 308 women and 399 men aged 26 years. Maximal heart rate during submaximal exercise was used to calculate VO_2 max. (ml/kg/min). Subjects were classified in tertiles of physical fitness according to VO_2 max. level. CRP was measured using an immunoturbidimetric assay.
Results: Geometric mean (95% CI) CRP levels were significantly related to levels of cardiorespiratory fitness in men (p<0.01) and women (p<0.001).

Cardiorespiratory fitness	Males (n=399)	Females (n=308)
Unfit	2.06 (1.69-2.49)	4.31 (3.57-5.17)
Intermediate	1.61 (1.34-1.92)	3.76 (2.97-4.70)
Fit	1.46 (1.18-1.77)	1.94 (1.53-2.42)

There was a significant fitness × sex interaction (p= 0.01) indicating the relationship was stronger for women. When adjusted for body mass index, blood pressure and smoking history the relationship was significant for women only.
Conclusions: CRP level is independently related to cardiorespiratory fitness in young women.

1028-174 Increased Subclinical Atherosclerosis in Young Adults With Metabolic Syndrome: The Bogalusa Heart Study

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Background
Metabolic Syndrome (MetS) is associated with subclinical atherosclerosis and increased cardiovascular risk in older and middle-aged adults, however these associations have not been studied among young adults. Carotid intima-media thickness (CIMT) is a validated measure of atherosclerosis that predicts cardiovascular events. The purpose of this study was to determine if MetS is associated with increased CIMT in young adults.
Methods
Non-diabetic subjects from the Bogalusa Heart Study, a longitudinal study of the natural history of atherosclerosis in young adults and children (20-38 years old), underwent high-resolution B-mode ultrasound imaging of the carotid arteries to determine site-specific and composite CIMT values. Presence of MetS was determined using the NCEP Adult Treatment Panel III definition. Logistic regression analyses were performed to determine if MetS was associated with increased CIMT.
Results
Of 506 subjects (mean age 32 years, 29% black, 39% male), 67 (13%) had MetS. CIMT values were significantly higher among subjects with MetS (table). The prevalence of MetS increased with CIMT (p_{trend} = 0.0028). Odds ratios (95% confidence intervals) for the presence of MetS in subjects with CIMT ≥0.8 mm and ≥1.0 mm were 4.8 (1.7-13.7) and 8.0 (2.0-32.8), respectively.
Conclusions
Even in young adults, MetS is associated with increased carotid atherosclerosis, emphasizing the importance of early screening and treatment in this population.

Mean Carotid IMT Values (mm, standard deviation)

	MetS Present	MetS Absent	$P_{unadjusted}$	P adjusted for age, sex, race, and smoking
Composite	0.780 ± 0.130	0.728 ± 0.097	0.0005	0.0016
Common Carotid	0.699 ± 0.108	0.659 ± 0.084	0.0008	0.0012
Bulb	0.922 ± 0.211	0.852 ± 0.174	0.0037	0.0222
Internal Carotid	0.721± 0.206	0.676 ± 0.121	0.0202	0.0384

POSTER SESSION

1029

Molecular Mechanisms for Hypertrophy and Failure

Sunday, March 07, 2004, Noon-2:00 p.m.
Morial Convention Center, Hall G
Presentation Hour: 1:00 p.m.-2:00 p.m.

1029-175 Anti-ErbB2 Modulation of Bcl-x_L/Bcl-x_S Causes Mitochondrial Dysfunction and Apoptosis

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Background
ErbB2 is a co-receptor and important signal integrator for the EGF family of receptor tyrosine kinases.Over expression of erbB2 occurs in many cancers. A monoclonal antibody inhibiting erbB2 is a potent chemotherapeutic agent but is associated with cardiac toxicity. Here we investigate the effects of anti-erbB2 antibody on cardiomyocyte survival and mitochondrial function.
Methods and Results
Primary cultures of neonatal were exposed to anti-erbB2 antibody (anti-erbB2 Ab 5-7.5 μg/ml) for up to 24 hours. Cell viability, mitochondrial function, and apoptosis were measured using multiple complementary techniques. Selected studies were confirmed in primary cultures of adult rat cardiomyocytes.
ErbB2 inhibition was associated with a dramatic increase in expression of the pro-apoptotic Bcl-2 family protein, Bcl-x_S, and decreased levels of pro-survival Bcl-x. There was a time dependent increase in mitochondrial translocation and oligomerization of the mitochondrial pore former, BAX, as indicated by BMH crosslinking. Bax oligomerization was associated with release of cytochrome c and activation of caspase 9.
This alteration of Bcl-2 family signaling induced mitochondrial dysfunction evident as a loss of mitochondrial membrane potential (delta psi) as measured by JC-1 red fluorescence on fluorescent plate reader (5242 ± 191 vs 4606 ± 87 p<.05 N=6) and by fluorescent flow cytometry of mitotracker stained NRVM (76.85 ± 2.4 vs 51.7 ± .072 p<.05 N=4). There was also a 35% decline in ATP level (p<.05) as measured by luciferin-luciferase bioluminescence and a loss of redox capacity as measured by MTT (.7224 ± .036 vs .6421 ± .017 p<.01).
Restoration of Bcl-x_L levels through TAT-mediated transduction prevented the decline in delta psi;, MTT activity and cytosolic ATP.
Anti-erbB2 Ab treatment resulted in a modest increase in apoptosis as measured by TUNEL (6.5± 0.7 vs 3.1 ± 0.4%. p<.05) and propidium iodide flow cytometry(8.3±0.9 vs 4.5±0.6 % p<.01)
Conclusion
Anti-erbB2 activates the mitochondrial apoptosis pathway through direct modulation of bcl-x_L and bcl-x_S and causes impairment of mitochondrial function, integrity, cellular energetics and low level apoptosis.

1029-176 Rescue of Internalization-Impaired Angiotensin II AT1 Mutants by β-Arrestin Overexpression

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The pathophysiological effects of Angiotensin II (Ang II) are mostly mediated by the G-protein coupled type 1 receptor (AT1), which internalizes upon Ang II binding. Recently, β-arrestin was shown to play a role in AT1 endocytosis by binding the cytoplasmic, C-terminus region T332-S338, the major site of Ang II-induced phosphorylation. The process responsible for recruiting β-arrestin to the activated receptor has not been defined. Using CHO-K1 and HEK 293 cells to express wild type or mutant AT1, we investigated whether T332-S338 phosphorylation is a prerequisite for β-arrestin-dependent AT1 internalization. We first established that phosphorylation of this region is important for AT1 internalization in our cells. Substitution of T332, S335, T336 and S338 with alanine to preclude phosphorylation, markedly attenuated AT1 internalization, while replacement of these sites with acidic residues glutamate (E) and aspartate (D) to mimic phosphorylation, partially rescued internalization. We next assessed the ability of β-arrestin overexpression to rescue agonist-induced internalization of phosphorylation-impaired receptors. β-arrestin 1 or 2 overexpression enhanced internalization of the TSTS/A mutant, with β-arrestin 2 having the more pronounced effect. β-arrestin 2, alone or with β-arrestin 1, increased the rate of TSTS/A internalization towards that of wild-type AT1. The TSTS/ED mutant was also responsive to β-arrestin 1 or 2 expression. These findings indicate that a signal besides C-terminus phosphorylation is responsible for recruiting β-arrestin to AT1. However, ligand-induced phosphorylation of AT1 likely facilitates receptor internalization by enhancing β-arrestin binding.